Comments on the National Toxicology Program (NTP) *DRAFT Report on Carcinogens: Substance Profile for Glass Wool Fibers (Respirable) as a Class*

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By way of background, I have extensive education and training in toxicology and experience in assessing the toxic and carcinogenic potential of natural and synthetic fibers (see attached list of fiber-related publications). I have a Bachelor's and a Master's degree in biology from the University of California at Los Angeles and a PhD in toxicology and pharmacology from the University of California at Davis. I conducted in vitro toxicity, neoplastic transformation, and genetic toxicology research on asbestos and synthetic vitreous fibers (SVFs)[1] while completing postdoctoral studies at the National Institute of Environmental Health Sciences (NIEHS). I continued these fiber studies using human bronchial epithelial cells grown in culture at the Chemical Industry Institute of Toxicology (CIIT—now the Hamner Institute). My next position was with Johns Manville where I spent 13 years conducting in vitro studies and overseeing a series of chronic rodent inhalation bioassays and biopersistence studies of asbestos and SVFs, sponsored by Johns Manville and other fiber manufacturers. Those studies provided a sound scientific basis for understanding the differences in pathogenicities of these diverse fiber types. I am currently employed by Navistar, Inc., a truck and engine manufacturing company, where my focus is on understanding the potential health risks of diesel exhaust.

In May, 2009, I was asked by NAIMA Canada to review and provide comments on the *Draft Report on Carcinogens Background Document for Glass Wool Fibers* (NTP, 2009a). I also provided oral comments at the NTP's Expert Panel Meeting on Glass Wool Fibers on June 9th and 10th, 2009 in Chapel Hill, NC (NTP, 2009b). More recently, I was asked by NAIMA

[1] Synthetic vitreous fibers is a generic name used to describe inorganic fibers manufactured primarily from glass, rock, minerals, slag, and processed oxides.

Canada to provide comments on the *Draft Report on Carcinogens: Substance Profile for Glass Wool Fibers (Respirable) as a Class* (NTP, 2010).

Executive Summary

On June 9th and 10th, 2009 the National Toxicology Program (NTP) convened an Expert Panel for glass wool fibers to review the scientific literature on the potential carcinogenic effects of glass wool fibers and make a recommendation for the listing status of these fibers in the 12th Edition of the Report on Carcinogens (NTP, 2009a; NTP, 2009b). As requested by NAIMA Canada, in May/June 2009 I provided written and oral comments to the NTP regarding the Report on Carcinogens Background Document for Glass Wool Fibers (Hesterberg, 2009). The 2009 NTP Expert Panel, which included fiber science experts, unanimously recommended that glass wool fibers, with the exception of special purpose fibers of concern, should not be classified either as known to be human carcinogens or reasonably anticipated to be human carcinogens (NTP, 2009c).

Disagreeing with its Expert Panel, the NTP recently released the Draft Substance Profile for Glass Wool Fibers (Respirable) as a Class (RoC GF), classifying all respirable glass wool fibers as "reasonably anticipated to be human carcinogens" (NTP, 2010).

This decision by the NTP to lump all glass fibers together and classify them as carcinogens is also in conflict with the 2002 classification of glass fibers by the International Agency for Research on Cancer (IARC, 2002). The 2002 IARC Monograph concluded that insulation glass wool was "not classifiable as to their carcinogenicity to humans." The IARC panel also concluded that special purpose fibers were "possibly carcinogenic to humans," which was similar to the recommendation of the NTPs Expert Panel when they met last year.

The NTP Draft Substance Profile description of the animal data gives equal weight to the results of intracavity injection studies as it does to well-conducted inhalation studies. This approach is contrary to a vast body of scientific research, which argues against the use of intracavity injection studies for either hazard or risk assessment. The numerous problems associated with this non-physiological method of exposure has led most fiber scientists to conclude that the results of these studies are not appropriate for evaluating the human health hazard or risk of fibrous dusts (OSTP, 1985; Eastes and Hadley, 1994; Collier et al., 1995; McClellan et al., 1992; McClellan and Hesterberg, 1994; McConnell, 1995; Rossiter, 1991). The major concerns follow:

- Target cells for the fibers that are injected or implanted into the peritoneal abdominal cavity are not the same as for respiratory tissues that are exposed via inhalation of fibers.

- Implantation/injection of fibers bypasses the natural defense mechanisms that are operative with inhaled fibers. For example, the upper airways naturally filter out larger fibers and prevent them from entering the deep lung; lung cells and mucous efficiently remove many of the fibers that are inhaled and deposited in the airways and in the deep lung.

- Very large fibers, which could not normally be inhaled into the lung, can easily be implanted or injected. Fibers with a large aerodynamic diameter are non-respirable, which means they have limited potential for becoming airborne and remaining suspended in the air and traveling with the inhaled air into the lower lung. Such non-respirable fibers are not relevant to the respiratory health of people. Nonetheless, these fibers have been injected into the body cavities of laboratory animals.

- IP or IT tests typically use very large quantities of fibers such that a substantial portion of the injected fibers tends to be concentrated at the injection site. With these large quantities, “Normal physiology, homeostasis and detoxification or repair mechanisms may be overwhelmed and cancer, which otherwise might not have occurred, is induced or promoted” (OSTP, 1985).

The 1985 findings of the U.S. Office of Science and Technology Policy (OSTP) were soon followed by similar conclusions from a number of authoritative national and international scientific bodies, including: the International Program on Chemical Safety (IPCS, 1988), National Institute for Occupational Safety and Health (NIOSH, 1977, 1987), the World Health Organization (WHO, 1992), the National Research Council (NRC, 2000) of the National Academy of Science, and the Agency for Toxic Substance and Disease Registry (ATSDR, 2004).

It is important to look, from a historical perspective, at how the glass wool fiber industry has worked with academic researchers and government agencies to assess the potential carcinogenicity of glass wool fibers. For many years, the glass wool industry recognized that its future success was dependent upon creating a proactive and comprehensive scientific research and product stewardship program for its fiber glass products. At the core was a comprehensive, large-scale research initiative to investigate the potential health hazards of fiber glass products. This initiative went well beyond routine testing of products and included research on the mechanisms by which adverse effects were or were not produced.

Epidemiological studies found no increase in the risk of mesothelioma or other cancers of the respiratory tract from occupational exposure to glass fibers. Inhalation toxicology studies in laboratory animals demonstrated that the glass wool fibers were less biopersistent and, thus, did not induce fibrosis and cancer as observed for certain types of asbestos and some biopersistent synthetic fibers. This scientifically sound and robust body of evidence on the potential health hazards of fiber glass has provided guidance for the safe manufacture and use of this product, including development of new more-biosoluble products that are inherently safer.

Independent scientists and government regulators were involved in all aspects of the investigations and the research findings were published in peer-reviewed journals. The information that was developed provided a scientific basis for the International Agency for Research on Cancer (IARC) to not classify insulation fiber glass as a possible carcinogen. Most importantly, as a result of the proactive product stewardship efforts glass wool products continue to be widely used and play an important role in conserving energy around the world.

Thus, there is a sound scientific basis for not classifying all glass wool fibers as carcinogenic. Classifying all glass wool fibers as carcinogens will have unintended negative consequences for both industry and the government agencies tasked with regulating glass fibers for the following reasons:

- The fiber glass industry has spent over 20 years on human epidemiology studies and high-quality animal inhalation studies, assessing the potential health effects of glass fibers and trying to understand the mechanisms of fiber toxicity. If this huge database is ignored, and all glass fibers are lumped together, even though there is much evidence for not lumping them, a message will be sent to all of industry (not just the glass fiber industry) that extensive health studies are not of value, because they will be ignored by the NTP.

- The fiber glass industry has also developed more biosoluble fibers to meet the EU criteria for not requiring a cancer warning label on products because of their increased solubility. The decision of the NTP to lump these more-biosoluble glass fibers with biodurable fibers and classify them all as carcinogens removes incentives to manufacture fibers that are less biodurable and inherently safer.

For these reasons, I strongly urge the NTP to reconsider its decision to classify all glass fibers as carcinogens. It would be more scientifically responsible to fully utilize the large body of scientific research on fiber glass, which has shown that most glass fibers are biosoluble in animal inhalation studies and do not produce fibrosis or cancer in well-conducted chronic inhalation studies. Only the special-purpose fibers of concern, which are more biodurable and produce cancer in well-conducted animal inhalation studies, should be classified as "reasonably anticipated" by the NTP. This differentiation of glass fibers and carcinogen classification is in harmony with both the IARC and the EU directive and with the recommendations of the NTP's own 2009 Expert Panel.

Cancer Classification of Glass Wool in the 2010 NTP Report on Carcinogens

The recently released *Draft Report on Carcinogens: Substance Profile for Glass Wool Fibers (Respirable) as a Class* (RoC GF) is unclear as to the proposed cancer hazard status of respirable glass wool fibers. While the RoC GF seems to classify glass wool fibers "as a class" as reasonably anticipated, the RoC also correctly notes that the "[c]arcinogenicity within the class of respirable glass wool fibers varies, and not all fibers within this class cause cancer." (NTP, 2010) This confusion in the classification of glass wool fibers is inconsistent with the weight of the scientific evidence, and is in conflict with the NTP's own 2009 Expert Panel, which unanimously recommended that glass wool fibers, with the exception of special fibers of concern, should not be classified either as known to be human carcinogens or reasonably anticipated to be human carcinogens (NTP, 2009c).

This draft RoC GF is also in conflict with the 2002 classification of glass wool fibers by the International Agency for Research on Cancer (IARC, 2002). The 2002 IARC Monograph concluded that insulation glass wool was "not classifiable as to their carcinogenicity to humans" (Group 3) (IARC, 2002, p. 339), which was based on "limited" animal evidence and "inadequate" human evidence (id., p. 338). The panel concluded that special purpose fibers were "possibly carcinogenic to humans" (Group 2B) (id., p. 339), based on "sufficient" animal evidence and "inadequate" human evidence (id., p. 338).

The 2002 IARC Monograph made important changes to the classification of glass wool compared to the 1988 Monograph. These changes resulted primarily because the induction of tumors by insulation glass wool fibers using the intraperitoneal (IP) test and other intracavity administration methods were balanced by the negative tumor findings in well-conducted chronic inhalation bioassays, resulting in a conclusion of only "limited" evidence for carcinogenicity of insulation glass wool fibers in animals. Induction of cancer by inhalation of special purpose fibers in well-conducted animal inhalation studies and other data was considered "sufficient" animal evidence for the carcinogenicity of special purpose fibers. The key components of a well-conducted animal inhalation study and why IP studies were not considered as relevant as well-conducted chronic inhalation bioassays will be described in detail below.

Historical Background of Industry's Approach to Assessing the Safety of Glass Fibers

It is important to look, from a historical perspective, at how the health assessment testing methodologies for glass wool fibers have advanced over the last 20 years to keep pace with changes in the scientific understanding of the mechanisms of fiber toxicity.

In the next two sections of these comments, I will review some of the early glass wool fiber toxicology studies and then describe the more recent, state-of-the-art studies, which were the centerpiece of a comprehensive scientific program to assess the potential carcinogenicity of glass fibers and other SVFs. These studies were conducted with scientific oversight by industry scientists and external scientific consultants. Moreover, regulatory authorities were kept informed of the research program and provided the opportunity to comment on protocols before the research was initiated. The research findings were presented at scientific meetings and published in peer reviewed journals.

Early Toxicology Studies in Laboratory Animals

Prior to 1987, laboratory research on the health effects of glass fibers and other inorganic fibers consisted primarily of studies in which fibers were injected into various body cavities of rats (Pott and Friedrichs, 1972; Stanton and Wrench, 1972; Stanton et al., 1977; Stanton et al., 1981). These early studies were largely intended to identify the effects of various kinds of asbestos fibers and to understand those fiber characteristics, especially diameter and length, which might be responsible for asbestos-induced disease. In those studies, fibers of various compositions and sizes were injected or implanted into the peritoneal cavity (abdominal intraperitoneal (IP) injection), the chest cavity (pleural space), or instilled into the trachea using a syringe (intratracheal instillation (IT)). The quantities of material injected or implanted were quite large. For example, Stanton et al. (1977, 1981) used a standard dose of 40 mg in gelatin pledgets for implantation into the pleural cavity. The 40 mg of test material would correspond to placing about 11 grams of fibrous material into the thoracic cavity of a 70 kg person.

Many of the implantation and injection studies reported an excess of tumors (sarcomas) in rats in glass fiber-treated groups as well as in the asbestos-treated groups following these types of implantation exposures. However, 43 out of 72 materials tested by Stanton et al. (1977, 1981) did not yield a statistically significant increase in tumors. This included 16 different glass preparations. Interpretation of the results of the early studies focused on the congruence between the findings of intra-cavity studies and the emerging epidemiological findings in asbestos-exposed workers. In short, the intra-cavity study findings provided a basis for interpreting the importance of fiber dimensions in the pathogenesis of asbestos-induced fibrosis (asbestosis), lung cancer and mesothelioma.

It was not until later that the experimental approach of using intra-cavity injections began to be critically evaluated. It was readily apparent that the exposure methods were non-physiological and differed markedly from the manner in which people might be exposed in the workplace or elsewhere, which is by inhalation of airborne fibers. The numerous problems associated with the non-physiological exposure methods led many scientists to conclude later that the results were not appropriate for evaluating the human health hazard or risks of fibrous dusts (OSTP, 1985; Eastes and Hadley, 1994; Collier et al., 1995; McClellan et al., 1992; McClellan and Hesterberg, 1994; McConnell, 1995; Rossiter, 1991). The major concerns were as follows:

- Target cells for the fibers that are injected or implanted into the peritoneal abdominal cavity are not the same as for respiratory tissues that are exposed via inhalation of fibers.

- Implantation/injection of fibers bypasses the natural defense mechanisms that are operative with inhaled fibers. For example, the upper airways naturally filter out larger fibers and prevent them from entering the deep lung; lung cells and mucous efficiently remove many of the fibers that are inhaled and deposited in the airways and in the deep lung.

- Very large fibers, which could not normally be inhaled into the lung, can easily be implanted or injected into experimental animals. Fibers with a large aerodynamic diameter are non-respirable, which means they have limited potential for becoming airborne and remaining suspended in the air and traveling with the inhaled air into the lower lung. Such non-respirable fibers are not relevant to the respiratory health of people. Nonetheless, these fibers can and often were injected into the body cavities of laboratory animals.

- IP or IT tests typically use very large quantities of fibers such that a substantial portion of the injected fibers tends to be concentrated at the injection site. With these large quantities, "Normal physiology, homeostasis and detoxification or repair mechanisms may be overwhelmed and cancer, which otherwise might not have occurred, is induced or promoted" (OSTP, 1985).

The 1985 findings of the U.S. Office of Science and Technology Policy (OSTP) were soon followed by similar conclusions from a number of authoritative national and international bodies, including the International Program on Chemical Safety (IPCS, 1988), National Institute for Occupational Safety and Health (NIOSH, 1977, 1987), the World Health Organization (WHO, 1992), the National Research Council (NRC, 2000) of the National Academy of Science, and the Agency for Toxic Substance and Disease Registry (ATSDR, 2004).

Thus, by the early 1990s, it was generally accepted that results observed in the non-physiological exposure studies cannot be assumed to be predictive of results that could occur in laboratory animal inhalation studies and, most importantly, in people exposed by inhalation.

By the early 1990s, it was also becoming increasingly accepted that inhalation exposure studies with well-characterized aerosols were the most appropriate method to evaluate human health hazards for airborne materials. The importance of conducting studies using inhalation exposures, as contrasted with non-physiological modes of administering fibers, was emphasized in the conclusions of multiple workshops (McClellan et al., 1992; McClellan and Hesterberg, 1994; Vu et al., 1996). McClellan (1995), in reviewing the role of experimental studies in informing human health risk assessments, emphasized the importance of exposing laboratory rodents via inhalation to airborne respirable fibers that are comparable in size to those found in the workplace air. Researchers in the field, such as Hesterberg and Hart (1994) also began to reference data on workplace exposure. (Table 1)

Table 1. Comparison of Fiber Exposures: Human Experience versus Rat Inhalation Study

Concentrations (Adapted from Hesterberg and Hart, 1994).

Environment	Product	Fibers/cm³
Human		
Outdoor	Fibers Related to Existing Insulation	0.0007
Indoor Air	Fiber Glass Batt Insulation, Prior to Installation	0.00005
Manufacturing	Fiber Glass Wool Insulation	0.065
Installation	Fiber Glass Batts Blowing Fiber Glass	0.09 7.67[2]
Removal	Ceiling and Pipe Insulation	0.04
Rat		
Inhalation Studies	MMVF-10, MMVF-11	239.

An important advance in the conduct of animal inhalation studies was the use of nose-only inhalation exposures as opposed to whole-body exposures (Bernstein et al., 1995). Nose-only exposures reduce the amount of size-separated fibers that need to be prepared for a study and also minimize the loss of fibers on the pelt of the animals and, thus reduce intake via ingestion from grooming. As an aside, in both laboratory animals and humans, some portion of inhaled fibers deposited in the upper airways are cleared to the oropharynx and ingested.

In the mid 1980s the glass fiber insulation industry sponsored a chronic (2 ½ year duration) nose-only inhalation study at Los Alamos National Laboratory in Los Alamos, NM, which was

[2] This level of exposure reflects available data in 1994. More recent exposure surveys indicate an average exposure level of 0.83 f/cc for blowing fiber glass (without binder). Marchant, Gary; Bullock, Christopher; Carter, Charles; Connelly, Robert; Crane, Angus; Fayerweather, William; Johnson, Kathleen; and Reynolds, Janis (2009) "Applications and Findings of an Occupational Exposure Database for Synthetic Vitreous Fibers," *Journal of Occupational and Environmental Hygiene*, 6:3, 143-150.

reported at the 1986 WHO Copenhagen meeting (Smith et al., 1987). Six different fibers were evaluated (four types of glass fibers, a refractory ceramic fiber (RCF), and a mineral wool fiber) in rats and hamsters. In those studies, none of the four types of glass fibers that were tested caused cancer. The RCF exposures resulted in one lung mesothelioma. The negative results in the Los Alamos study were questioned by some observers, because the individual fibers in the exposure aerosol were on average shorter than the lengths of fibers typically found in workplace air. This likely occurred as a result of the process that was used to generate the aerosol in the study. It is now well known that fiber length is an important determinant of fiber pathogenicity.

The IARC (1988) Monograph classified glass wool fibers as “possibly carcinogenic to humans” (Group 2B), based on “sufficient animal evidence” and “inadequate human evidence” (IARC, 1988). In this early evaluation, the intraperitoneal (IP) injection test results were given substantial weight. Those results were not balanced by results of inhalation bioassays, because the inhalation studies reported up to that time were neither well designed nor conducted to the rigorous standards that were introduced later. The IARC (1988) Monograph did not subcategorize glass wools into insulation glass wool fibers and special purpose fibers (SPFs), as was done in the subsequent IARC (2002) Monograph. This did not occur in 1988 because there was not enough data on which to base a differentiation of the two glass wool types and provide a separate cancer hazard evaluation. SPFs are highly engineered glass fibers typically used for non-insulation purposes, such as air filtration and battery separator media.

By way of comparison, IARC (1988) classified several forms of asbestos (actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) as “carcinogenic in humans” (Group 1) based on “sufficient human evidence.” Since the synthetic fibers were evaluated by the same panel of experts evaluating the several kinds of asbestos, it is reasonable to speculate the findings for asbestos, and especially the weight given to the IP test results, may have had a negative “halo” effect on interpreting the significance of the IP results as predictors of the carcinogenicity of synthetic fibers. IARC also determined that reinforcement glass fibers were in Group 3, not classifiable. This was because those fibers have such large diameters that they are not respirable.

More Recent State-of-the-Art Rodent Inhalation Studies

The conclusions of the IARC (1988) review made it clear that new animal toxicity studies would be needed to resolve questions about the Los Alamos study and concerning the value of non-inhalation animal studies.

Prior to 1988, studies of glass fiber toxicology using the rodent inhalation model had serious technical limitations. These included: use of test fibers that were too thick to be readily inspired into the deep lung and/or were too short to have unique carcinogenic properties; inadequate characterization of fiber numbers and dimensions in exposure aerosols and/or inadequate reporting; lack of measurement of the burden of fibers in the lungs; and the absence of a determination of whether the Maximum Tolerated Dose (MTD) had been attained. The MTD is the highest daily dose that does not cause overt toxicity in a ninety-day laboratory study. The MTD is used in longer studies to maximize the likelihood of detecting any toxic effect including cancer (McConnell, 1996).

Recognizing these technical limitations, the fiber insulation industry designed and sponsored studies that addressed and corrected them. The basic design of the studies built on the experience gained in the National Toxicology Program and by other organizations in conducting carcinogenicity bioassays. Moreover, the studies made use of improved aerosol science and inhalation toxicology capabilities that were emerging (McClellan, 2000).

In planning the new studies, the industry sought to meet or exceed the highest contemporary scientific standards. To assist in ensuring the quality of the research, a Science Advisory Group (SAG) was convened to help design the SVF research program, to provide oversight of the research and to aid in interpretation of the results. The SAG members were respected independent experts in the fields of medicine, veterinary medicine, public health, toxicology, epidemiology, aerosol science, industrial hygiene, and statistics. The study results as they became available were shared with the scientific community, regulators, workers, and the public and also presented at scientific meetings and published in peer-reviewed scientific journals.

To evaluate the potential for a material to cause tumors or other effects of any kind, chronic inhalation exposure studies must have multiple exposure levels. The highest exposure concentration is selected to maximize the potential for detecting an excess of effects over that observed in controls. At the same time, it is important to avoid having an exposure level that is so high that non-specific toxic effects are produced that may interfere with the detection of test agent specific effects. Selection of the appropriate highest exposure level (the Maximum Tolerated Dose) is always challenging (Lewis et al., 1989; McClellan et al., 1992; Hesterberg et al., 1999).

The issue of conducting studies with aerosol exposures that might exceed the MTD came to the forefront in the 1980s with the observation of a high incidence of lung tumors in rats exposed to materials that were not genotoxic or were suspected of having low genotoxic potency. Of special note were findings from multiple studies conducted with whole diesel exhaust in which an excess of lung tumors was observed in rats, but not in mice, exposed to the same test atmosphere (Mauderly et al., 1987, 1996; Hesterberg et al., 2005; Mauderly and Garshick, 2009). Detailed studies on the deposition and retention of the diesel soot (carbonaceous particles and associated hydrocarbons) demonstrated that the retention of the inhaled particles was altered when the rats were exposed to high concentrations of particles (up to 7 mg/m^3, 7 hours/day, 5 days/week) (Wolff et al., 1987). The resulting "lung overload" led to a cascade of events including inflammation, cell proliferation, mutations, and ultimately, lung cancer. Similar findings were observed with carbon black, titanium dioxide, and talc, which are free of any direct acting mutagenic chemicals. The National Toxicology Program, recognizing that the issue of "lung overload" was of broad concern, convened a special panel to offer advice on setting aerosol exposure concentrations for inhalation toxicity studies (Lewis et al., 1989).

An awareness of the experience with "lung overload" and "maximum tolerated dose" with non-fibrous aerosols stimulated rigorous consideration of these issues in planning the new generation of fiber inhalation studies (Hesterberg et al., 1996b). The planning and conduct of the new fiber studies also addressed other technical limitations noted in previous studies, frequently by incorporating innovative approaches. These included:

- *Use of Size-separated fibers*. It is now well known that fiber length and diameter are critical determinants of the toxicity of durable fibers—longer fibers (greater than 15 μm) were more toxic, and thinner fibers (less than 2 μm in diameter) were more respirable. Some earlier chronic inhalation studies were conducted using relatively short test fibers and/or fibers that were too thick to allow a substantial portion of the fibers inhaled to be deposited in the lungs. Thicker fibers deposit predominantly in the upper respiratory tract with, at best, only a small portion reaching what is viewed as the more vulnerable deep lung. Typically, the vast majority of fibers in glass wool insulation are too thick and long to be readily respirable. Techniques were developed to break the glass fibers and then selectively separate out the longer thinner fibers. Thus, the fibers prepared for use in the inhalation studies represented only that portion of the total mass thought to have the highest potential for producing effects. Fibers observed in sampling workplace air were found to typically have an average diameter of 1 μm and an average length of 20 μm. Thus, techniques were developed to select fibers with these dimensions and prepare large quantities for use in animal exposure studies. The size selection techniques were highly innovative and produced consistent fiber sizes for a number of different glass fibers and other synthetic vitreous fiber compositions. Thus, it was possible to compare the lung effects of the various different fiber compositions in rats exposed by inhalation while minimizing the confounding variables of fiber length and diameter (Hesterberg et al., 1993). The likelihood of inhaled fibers transiting the branched and narrow conducting airways of the respiratory tract and reaching the deep lung is determined by the inertial properties of the fibers. The inertial property of particles of different shapes and densities is characterized by their "aerodynamic diameter," a comparison of their inertial properties to that of a spherical particle having a density of 1 gm/cm^3. Thus, it is important to characterize the fibers to which the test animals were exposed as to their aerodynamic diameter as well as to their fiber number and dimensions.

- *Quantitative reporting of fiber numbers and dimensions in aerosols*. The methods used allowed the aerosols to be characterized with regard to fiber dimension, number of fibers/cc of air as well as more typical measures of particle mass reported as mg/m^3.

- *Lung burdens.* Techniques were developed to characterize by number and fiber dimension the lung burden of fibers. This allowed results to be analyzed not only with regard to exposure concentration, as was traditional, but also as to the number of fibers deposited in the deep lung (lung dose). This facilitated the evaluation of the deposition and clearance of the inhaled fibers and, ultimately, a comparison of various kinds of fibers based on their biopersistence in the lung.

Chronic inhalation studies

The North American Insulation Manufacturers Association (NAIMA) sponsored a series of inhalation studies, conducted at Research and Consulting Company (RCC) (an independent contract research laboratory in Itingen, Switzerland) over ten years, which were at the core of the industry's Product Stewardship program. We recognized that well-conducted inhalation studies with fibers known to be carcinogenic to humans were needed to validate the protocol being used to evaluate the carcinogenic potential of the synthetic fibers. Thus, the core program included animal groups exposed to amosite and crocidolite asbestos, anticipating that these fibers, known to be human carcinogens, would produce an excess of tumors in laboratory animals. In addition, nine different synthetic fiber types were studied (Table 2) (Bernstein et al., 1996, 1997; Hesterberg et al., 1993, 1997, 1998a, 1998b, 1999; Hesterberg and Hart, 2001; Mast et al., 1995a, 1995b; McConnell et al., 1994, 1999). The United States Environmental Protection Agency (US EPA) and the Occupational Safety and Health Administration (OSHA) were invited to comment on the study protocols before the studies were initiated to ensure the results, irrespective of whether an excess of tumors were or were not observed, would be accepted for regulatory purposes. These agencies were also provided with the interim study results as they became available and the final reports and published papers.

Table 2. Lung Deposition, Biopersistence, and In Vitro Dissolution of SVFs Correlated with Lung Pathogenicity[a]

Fiber	Type	Lung Deposition		Lung Clearance	In Vitro Dissolution		Pathogenicity		Reference
		F/L x 10^6 ± st. dev		F >20 μm	pH 7	pH 4.5	Chronic Inhalation		
		F/L >5 μm	F/L >20 μm	$WT_{1/2}$[b] (days)	K_{dis}[c]	K_{leach}[d]	Fibrosis	Tumors	
Amosite	Asbestos	10.9 ± 1.0	1.6 ±0.3	418	<1	nd[e]	+	+	McConnell et al., 1994
Crocidolite	Asbestos	29.8 ±7.1	1.0 ±1.0	817[f]	<1	nd	+	+	McConnell et al., 1994
MMVF32	Special Purpose E Glass	5.7 ±1.3	1.3 ±0.3	79	9	7	+	+	Davis et al., 1996
RCF1a[f]	Refractory	8.3 ±2.0	1.5 ±0.2	55	3	nd	+	+	Mast et al., 1995a
MMVF33	Special Purpose 475 Glass	7.1 ± 0.6	1.4 ±0.3	49	12	13	+	+/–[g]	McConnell et al., 1999
MMVF21	Rock Wool	7.7 ±1.0	1.1 ±0.1	67	20	72	+	–	McConnell et al., 1994
MMVF10	Insulation Glass Wool	8.6 ± 1.6	1.0 ± 0.2	14.5[h]	300	329	–	–	Hesterberg et al., 1993
X607[e]	Hybrid SVF	3.6	nd	9.8	990	nd	–	–	Hesterberg et al., 1998a
MMVF11	Insulation Glass Wool	5.6 ±1.2	1.0 ±0.2	9	100	25	–	–	Hesterberg et al., 1993
MMVF22	Slag Wool	3.4 ± 0.6	0.4 ±0.1	9	400	459	–	–	McConnell et al., 1994
MMVF34	Stonewool	9.1 ± 1.7	1.5 ±0.4	6	59	1010	–	–	Kamstrup et al., 1998

Notes

[a] Table from Hesterberg and Hart, 2001, and Hesterberg et al., 1998b.

[b] $WT_{1/2}$ = weighted clearance half-time in days.

Notes (continued)

[c] k_{dis} (dissolution rate, k_{dis} = ng/cm^2 hr) values for MMVF34 from Kamstrup, et al., 1998; others from Eastes and Hadley, 1994. K_{dis} values may differ from those published elsewhere due to varying methodologies.

[d] k_{leach} Dissolution rate constant of leaching elements represented by Ca and Mg at pH 4.5 (rounded up to whole numbers). Source: Guldberg et al., 1998.

[e] nd = not done

[f] RCF1 was used in pathogenicity studies. RCF1a was modified from RCF1 to contain fewer non-fibrous particles.

[g] +/– indicates tumorigenicity in hamsters (one mesothelioma in 83 animals) but not in rats.

[h] Clearance half-time of 14.5 days was determined using a modified MMVF10 test fiber that had been size-selected to have longer and thinner average dimensions than the original MMVF10.

The basic protocol for the chronic studies involved nose-only exposure (6 hours/day, 5 days/week) of rats and Syrian hamsters for up to two years with animals monitored for the rest of their lives. Rats were selected because the rat is the species most frequently used in inhalation studies with airborne particulate materials, thus allowing direct comparison to other relevant studies. Syrian hamsters were used primarily because they had been used in the earlier industry studies conducted at the Los Alamos National Laboratory in the 1980s, which are described above. Moreover, Syrian hamsters were being used increasingly in inhalation studies with airborne particulate materials. Mice were not considered appropriate because their relatively small airways limit the upper bound of the size of particles that can be tested (Snipes, 1989).

The fiber aerosols were produced using a special aerosol generation system developed at the Research and Consulting Company, Geneva, Switzerland (Hesterberg et al., 1993; Bernstein et al., 1994). The animals were exposed nose-only in an engineered exposure system (Cannon et al., 1983) that provided for continuous laminar flow of the air past the nose of each animal and with exhaled air diverted so it did not reach other animals being exposed concurrently. The fiber concentrations were monitored continuously with a light-scattering instrument. Fiber mass measurements were made with membrane filters. In addition, samples were collected periodically for electron microscopic determination of fiber dimensions. The target aerosol concentrations for the fiber glass exposure groups were 3, 16 and 30 mg/m^3.

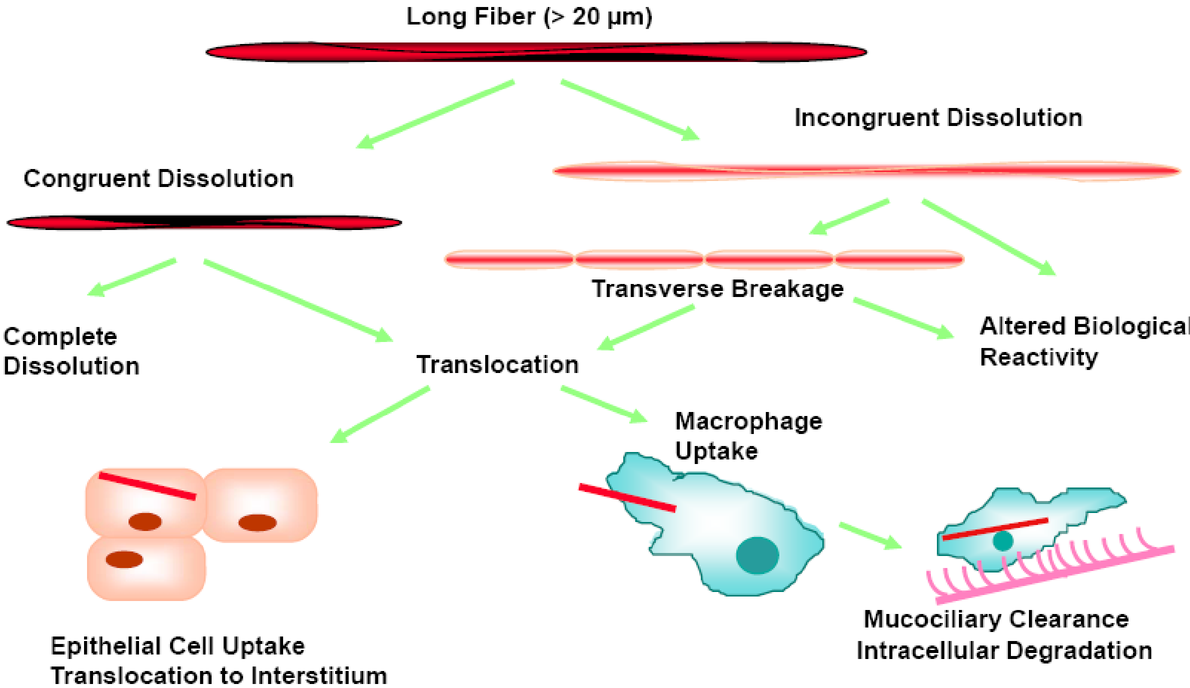
Health indicators were routinely evaluated. Detailed gross and histopathological evaluations of the respiratory tract were included. Sub-groups of animals were periodically sacrificed and lungs examined to determine the fiber burden (Hesterberg et al., 1996b). The lungs were dried and plasma ashed to provide specimens for quantification of the fiber lung burdens and determination of fiber dimensions.

In the RCC chronic inhalation studies, the five glass wool insulation fibers, which had low biopersistences, caused no lung fibrosis or tumors even when laboratory animals were exposed to high concentrations of long, respirable fibers. The results of the other synthetic vitreous fiber (SVF) inhalation studies demonstrated that "biopersistence" was the key determinant of the toxicity of SVFs (Bernstein et al., 1994; Hesterberg et al., 1996b). Biopersistence refers to the ability of the fiber to persist in the lung over time. Some types of SFVs produced an excess of lung tumors under the conditions of the bioassay. From a broader perspective, the positive tumor findings in the two asbestos groups (amosite and crocidolite) and two of the synthetic fiber groups (Special Purpose Fibers and Refractory Ceramic Fiber) validated the bioassay as being capable of detecting tumorgenic activity. The finding of both positive and negative tumor outcomes led the fiber industry to initiate additional experiments to gain a better understanding of the importance of biopersistence in determining the lung disease causing potential of SVFs.

Short-term biopersistence studies

In the chronic inhalation studies, fiber biopersistence, which is dependent on chemical composition and manufacturing mode, was an important determinant of fiber pathogenicity. Fiber dissolution is a measure of how quickly a fiber dissolves in a simulated body fluid in a test tube (*in vitro*). It was hypothesized that fiber dissolution rates could serve as a surrogate for the more relevant parameter, biopersistence in the lung (Bernstein et al., 1994; Hesterberg et al., 1998a,b; Hesterberg and Hart, 2000). Biopersistence measures how long a fiber can persist after being deposited in the lung. Some fibers crumble (break transversely) and/or dissolve relatively quickly in the lung environment, while other fiber types persist for longer periods or even appear to be indefinitely retained (see Figure 1).

Figure 1. Fiber biopersistence is determined by dissolution, leaching, and fragmentation.



In order to understand the actual fate of inhaled fibers in the lung, protocols were developed for measuring biopersistence in the rat lung (Bernstein et al., 1994; Hesterberg et al., 1996a; Hesterberg and Hart, 2001). These studies were designed to track the number and dimensions of fibers retained in the lung over time. In the biopersistence studies, rats were exposed by nose-only inhalation techniques for five days (six hours per day) to the same fibers used in the chronic inhalation studies (nine different SVFs and two asbestos types), and then held without further exposure. At several points up to one year after exposure, the lung burdens (including fiber number, and bi-variate length and diameter) were evaluated.

The different fiber types were compared based on how long it took to clear half of the original fibers from the lung. A metric, the weighted lung clearance half-time ($WT_{1/2}$), was developed to compare the clearance rates of different fiber types from the lung. Based on this work, it was found that the single parameter, $WT_{1/2}$, correlated very well with the toxicity produced by the fibers (Table 2). Therefore, the $WT_{1/2}$ values could be used as a surrogate for the relative toxicity and carcinogenicity of fibers.

These biopersistence studies were critical to understanding why some fibers produce pathogenic changes and others do not. A major goal of the research effort was to determine whether the results of short-term biopersistence tests were valid predictors of long-term toxicity and carcinogenicity. Biopersistence studies require fewer animals and can be completed within a few months, compared to lifetime chronic carcinogenicity studies, which cost millions of dollars, utilize hundreds of animals, and take several years to complete (Hesterberg and Hart, 2001). Moreover, the quick turn-around associated with short-term tests is an important factor when new fibers are being developed and considered for commercial introduction.

The European Commission (EU, 1997), taking cognizance of the biopersistence results, adopted a formal directive for not classifying fibers as carcinogens if they meet certain criteria. Specifically, the classification as a carcinogen need not apply if it can be shown by a specific protocol that a fiber passes one of the following tests in specific EU-approved protocols:

- A short-term biopersistence test by inhalation has shown the fibers longer than 20 µm have a weighted half life less than 10 days, or
- A short-term biopersistence test by intratracheal instillation has shown that the fibers longer than 20 µm have a weighted half-time less than 40 days, or
- An appropriate intra-peritoneal test has shown no evidence of excess carcinogenicity, or
- Absence of relevant pathogenicity or neoplastic change in a suitable long-term inhalation test.

The adoption of this formal directive served as a major stimulus to European (and U.S.) SVF manufacturers in developing, testing, and then marketing synthetic glass fibers, which had low biopersistences and could meet the criteria for low biopersistence. The European Commission (EU, 1997) Directive encouraged the manufacture of low biopersistence, and hence safer, fibers both in the EU and in other markets around the world.

Why did the earlier intra-cavity implantation studies show positive tumor results for some non-biopersistent SVFs?

Some of the studies in which rodents were exposed by implantation of fibers into the trachea, chest cavity, or abdominal cavity did show positive results for some of the SVF insulation wools. The results were in sharp contrast to the results of the chronic inhalation studies. Most fiber toxicology researchers now explain the positive results from the non-inhalation exposure studies as a result of the implantation mode of administration by-passing the respiratory system's numerous defense mechanisms. These defense mechanisms include the convoluted upper airways that filter out most of the fibers, which are then cleared by the ciliated mucosa before they can reach the vulnerable deep lung. The deep lung, although it lacks a ciliated mucosa, has specialized mobile cells (macrophages) that engulf particles and carry them up to the airways, where the ciliated mucosa then sweeps them up to the throat, and they are swallowed or expectorated. The pleural space of the lung and abdominal mesothelium, where fibers are injected in the intra-cavity fiber studies, do not have these defense mechanisms. Thus, fibers, which have been deposited directly in these body cavities, cannot be efficiently cleared. This, together with the large quantities administered by intra-cavity implantation, result in tissues being overloaded with fibers, and especially aerosol surfaces. Thus, it is not surprising that even non-biopersistent fibers and other innocuous dusts have been found to cause fibrosis and tumors by these non-physiological routes of exposure (Roller et al., 1997).

In vitro studies

In vitro studies are conducted in "test tubes," or more accurately now, in a variety of plastic laboratory containers. As compared to inhalation studies in laboratory animals, *in vitro* studies are very inexpensive to conduct. Thus, hundreds of laboratories around the world can conduct such studies compared with only the few that are capable of conducting fiber inhalation studies. *In vitro* studies use living cells growing in culture dishes or in simulated biological fluids. Both types of studies were conducted in Johns Manville (JM) research laboratories to better understand how fibers might affect human health. As will be described later, the conduct of *in vitro* studies was strongly influenced by my having conducted such studies earlier at the National Institute of Environmental Health Sciences (NIEHS).

In vitro cell culture studies

In the 1980s, numerous laboratories in the US and other countries were studying the toxicity of asbestos and other fibers *in vitro*, that is, in cultured cells. Cells were extracted from the tissues of laboratory rats or mice and grown in culture dishes. Some cells were treated with chemicals or viruses to enhance their longevity and proliferation in culture and the ability to produce serial cultures. Other cultures were primary cells that were taken directly from the animal and were more difficult to grow in culture.

The 1970s and 1980s were a period of major advances in cell and molecular biology. There was great enthusiasm for using the emerging techniques for detecting alterations in cells caused by toxic agents and for using the new approaches to screen new agents for toxic effects. The NIEHS devoted substantial resources within their intramural research program to advance the use of cellular and molecular approaches to studying genotoxic effects. As a Postdoctoral Fellow at the NIEHS in the laboratory of Carl Barrett, I participated in research on chromosomal mutations and cell transformation in mammalian cells treated with asbestos fibers and other mineral dusts (Barrett et al., 1983; Barrett et al., 1984; Bernstein et al., 1996; Hesterberg and Barrett, 1984; Hesterberg and Barrett, 1985; Hesterberg et al., 1985; Hesterberg et al., 1986; Oshimura et al., 1984; Oshimura et al., 1986). At that time, the research team thought we were on the trail of identifying key events induced by asbestos fibers that were responsible for the carcinogenic effects observed in workers. It was easy to envision that the *in vitro* mutagenicity assays could be used to screen SVFs being considered for commercial introduction. Such short-term assays, i.e., the well-known Ames Test (Ames et al., 1973), were being greeted with enthusiasm. In retrospect, some of the *in vitro* research findings were possibly over-interpreted. Based on today's knowledge, the quantities of asbestos fibers used in many of the cell culture studies were massive when compared to even the highest inhalation exposure. It is also now apparent that the design of these studies could have been improved if a substantially broader range of exposure (dose) concentrations had been tested and greater effort had been expended in linking the dose used in the *in vitro* studies to *in vivo* doses actually encountered by tissues following inhalation exposure of people or laboratory animals. In the absence of that hindsight, it seemed reasonable in the 1980s to use the methods that had proved successful with asbestos fibers to study SVFs. In short, would similar toxicologic effects be observed?

Accordingly, in 1989 we at JM constructed a complete state-of-the-art *in vitro* cell biology laboratory and initiated cellular toxicology studies with fibers. Over the next eight years, I conducted a series of studies in which various types of cultured cells were exposed *in vitro* to the same size-selected SVFs and asbestos fibers that were being tested in the rat and hamster inhalation studies, as well as to numerous other fiber sizes and compositions (Hart et al., 1994; Hesterberg and Hart, 2001). In these studies, for all the fiber compositions tested, cytotoxicity (cell death or failure to proliferate) and genotoxicity (disruption of the nuclear material, i.e., the genetic material) were directly proportional to fiber number per cell and fiber length. Longer fibers were more toxic than shorter fibers, no matter the composition of the fibers studied (Hart et al., 1994). This consistent finding of cellular effects was in striking contrast to the results of the chronic rodent inhalation studies with SVFs. Recall that six of the nine different SVFs studied did not cause lung fibrosis and seven of the nine synthetic fibers did not produce tumors. Because all fibers compositions were toxic in the cell culture studies, it was clear that the *in vitro* cell culture models generated false positive results. It is clear that the results of the *in vitro* assays should not be considered valid for assessing human health hazards or risks from SVFs (Hesterberg and Hart, 2001). Some scientists have argued that information gained from *in vitro* studies with fibers can provide useful insight into the mechanisms that cause toxicity and, indeed, tumors. Now that the importance of biopersistence to fiber pathogenicity is understood, the *in vitro* cellular approach to understanding the potential of fibers to induce cancer can be considered obsolete. Indeed, it may be that interpretation of genotoxicity effects as the key step in fiber carcinogenicity in the early studies with asbestos fibers served to deter progress in the field.

The biopersistence studies demonstrated that, in the whole animal, fiber dissolution, breakage, and lung clearance remove the non-biopersistent fiber constituents from the lung. This provided a rational explanation for why some fiber compositions do not cause lung cancer or fibrosis, even at very high exposure concentrations. As with the intra-cavity implantation studies, *in vitro* cell culture models do not include the natural filtration and clearance mechanisms found in the whole animal that has been exposed naturally by inhalation of fibers.

In vitro fiber dissolution studies

In vitro fiber dissolution was another field in which major contributions were made by researchers at fiber industry laboratories. In these studies, researchers developed methods to determine the rate of dissolution and breakdown of fibers *in vitro* in simulated biological fluids. The fluids simulated both lung extracellular fluid and the more acidic intracellular lysosomal environment of alveolar macrophages, which assist in clearing the lower lung of inhaled debris (Eastes and Hadley, 1994, Bauer et al., 1994). The results of these *in vitro* studies showed reasonably good correlation with the results of the rodent inhalation biopersistence studies (Table 2). Again, the *in vitro* fiber dissolution studies contributed to a better understanding of fiber biopersistence and degradation in the lung. However, the results did not correlate as well to the results of the rodent chronic inhalation carcinogenicity studies as did the results of the biopersistence studies. Chronic exposure to SVFs or any of the fibers with low biopersistence produced neither tumors nor fibrosis in animal inhalation studies (Table 2).

The short-term biopersistence protocols approved by the EU (Bernstein and Riego-Sintes, 1999; Hesterberg et al., 2002) proved valuable in guiding the development of new fiber formulations.

2002 IARC Re-evaluation of Glass Fibers

In 2002, IARC published a reevaluation of the carcinogenic risk of SVFs (IARC, 2002). For purposes of hazard determination, the IARC panel differentiated the glass wool category into two separate SVF categories, insulation glass wool and special purpose fibers. The IARC decision to divide glass wool into two categories was based on the large number of well-conducted animal chronic inhalation carcinogenicity and biopersistence studies that were done between 1987 and 2001 (summarized in Table 2). These studies clearly showed that special purpose fibers were carcinogenic in animals by inhalation exposure, while insulation glass wools were not, which was readily explained by differences in the biopersistence in the lung of these two fiber types.

Importantly, the human epidemiology data for both glass fiber types was determined to be insufficient.

The 2002 IARC Monograph thus made some important changes in the classification of glass wool compared to the 1988 Monograph. These changes resulted primarily because the induction of tumors by insulation glass wool fibers using the intraperitoneal (IP) test and other intra-cavity administration methods noted earlier by IARC (1988) were now outweighed by the new negative tumor findings in well-conducted chronic inhalation bioassays that had been validated for their ability to detect tumor responses elicited by fibers. This resulted in the IARC panel of fiber toxicity experts concluding there was only "limited" evidence for carcinogenicity of insulation glass wool fibers in animals. Also, the new finding that cancer in experimental animals resulted from inhalation of special purpose fibers in a well-conducted animal inhalation study, coupled with mechanistic data, was considered "sufficient" animal evidence for the carcinogenicity of special purpose fibers. The 2002 IARC Monograph concluded that insulation glass wool fibers were "not classifiable as to their carcinogenicity to humans (Group 3)" (IARC, 2002), which was based on "limited" animal evidence and "inadequate" human evidence (Ibid., p. 338). The panel concluded that special purpose fibers were "possibly carcinogenic to humans (Group 2B)," based on "sufficient" animal evidence and "inadequate" human evidence (Table 3).

Table 3. The Re-evaluation of Fiber Glass by IARC in 2001 (IARC 2002).

Fiber	Human evidence	Animal evidence	1988 Classification	2002 Classification
Glass wool	Inadequate	Limited	Group 2B: possibly carcinogenic	Group 3: not classifiable
Special purpose fibers such as MMVF33 (475)	--	Sufficient	Group 2B: possibly carcinogenic	Group 2B: possibly carcinogenic

The IARC panel also noted the existence of newly developed fibers designed to be less biopersistent, including the alkaline earth silicate or high-alumina, low-silica wools. However, the panel elected not to make an overall evaluation of those new fibers in part because no human data were available, although the fibers that had been tested appear to have low carcinogenic potential in experimental animals.

Summary and Conclusions

As of the mid 1980s, the state of the science in fiber toxicology was not well developed. Different approaches to fiber testing produced seemingly contradictory results.

There were numerous problems with early laboratory research on glass fibers and other SVFs. As noted, these studies often used non physiological exposure routes such as intraperitoneal, intrapleural, or intratracheal injection of massive quantities of fibers. The fiber insulation industry, with oversight from independent scientific experts, designed and sponsored studies that systematically addressed and corrected these limitations and provided data that were more relevant for assessing the potential health hazards of exposure to airborne fibers. The chronic inhalation exposure studies conducted in rats and Syrian hamsters demonstrated that biopersistence was the key determinant of the toxicity of SVFs. Glass insulation wools, which had low biopersistences, did not cause lung fibrosis or tumors, while the more durable and biopersistent man-made fibers (an industrial refractory ceramic fiber and a special pupose fiber) caused increased incidences of fibrosis and tumors in animals. Fiber clearance rates determined from short-term inhalation studies were found to correlate very well with fiber pathogenicity. An understanding of the determinants of toxicity and carcinogenicity has provided a scientific basis for developing and introducing new safer products. The availability of short-term test methods has greatly facilitated development of new fibers.

The finding that the results of *in vitro* cell culture studies were not predictive of the results of the chronic rodent inhalation studies was important. This indicated that the *in vitro* cell culture models generated false positive results. It is clear that the cell culture results should not be considered valid for assessing human health hazards, and most certainly not risks, from SVFs. In contrast, the results of *in vitro* fiber dissolution studies, which measure fiber dissolution and breakage in simulated biological fluids, were good predictors of the *in vivo* fate of fibers in the rodent inhalation biopersistence studies.

This rigorous approach to understanding glass fiber toxicology provides an important perspective for the growing use of short-term test methods, based on modern biology, to evaluate the potential toxicity of chemicals and other agents (NRC, 2007). At least two important lessons emerge from the glass fiber experience. First, realistic doses must be selected for evaluation in *in vitro* assays. Unrealistic doses can yield results that appear mechanistically plausible. The development of mechanistic data with high levels of *in vitro* exposure does not necessarily mean the observed mechanisms are likely to occur as a result of lower levels of exposure expected to be encountered by workers or the general public. Second, it is important that tests, whether they be *in vitro* assays such as those used to evaluate mutagenicity, short-term animal tests to evaluate biopersistence or chronic animal bioassays to evaluate carcinogenicity, need to be evaluated for their predictive capability using both materials known to be human toxicants and materials demonstrated to have an absence of human toxicity. For certain kinds of SVFs, a convincing body of epidemiological evidence was available, demonstrating that glass fibers were not carcinogenic. This human data, both positive and negative, was of immense importance in validating the predictive capacity of the chronic inhalation bioassay protocol and the biopersistence protocol. Most importantly, it is now clear that what once were thought to be biologically plausible, mechanism-based results from certain *in vitro* studies yielded misleading findings for predicting human hazards.

By the turn of the century, the state of the science in fiber toxicology had progressed from a tangle of contradictory theories to clear understanding of the behavior of fibers in the lung. *In vitro* dissolution studies can now be used to predict the biopersistence of fibers in well-designed and well-conducted animal inhalation studies. Most importantly, these advances in the science provide a basis for understanding which fibers would have the potential for producing disease.

To assure that these new research findings were available and considered by hazard determination agencies and regulatory bodies, industry made certain that new results were promptly available to regulatory authorities and to agencies such as IARC that develop hazard determinations that guide regulatory agencies. This active involvement buttressed with high quality research published in peer-reviewed scientific journals should encourage a more balanced response by regulatory bodies and related organizations such as IARC, OSHA, NTP, ACGIH, and the EU.

The most significant outcome of this substantial research effort is that the public can be assured that glass fiber products, when used appropriately, are safe. Importantly, the research findings have led to changes in the composition of fibers and the manufacturing process such that the glass fiber products marketed today are even less biopersistent, if inhaled, than earlier glass fiber products and, thus, can be viewed as safer. Public confidence in the safety of glass fibers used as an insulating material is especially important in today's economy with its emphasis on energy efficiency.

Thus there is a sound scientific basis for not classifying all glass wool fibers as "reasonably anticipated." For the following reasons, classifying all glass wool fibers as potential carcinogens would have unintended negative consequences for industry, government agencies tasked with regulating glass fibers, and the public: (1) a message will be sent to all of industry (not just the glass fiber industry) to not invest in high-quality health studies, because they will be ignored; (2) a decision to lump these more-biosoluble glass fibers with biodurable fibers and classify them all as carcinogens diminishes the incentives to manufacture fibers that are less biodurable and safer; and (3) most importantly, classifying all glass wool fibers as potentially carcinogenic sends a strong signal that biosoluble fibers have the same hazard as biodurable fibers, a result that is not only scientifically incorrect but is also anathema to the mission of the NTP.

For these reasons, I strongly urge the NTP to reconsider its initial decision to classify all glass fibers as carcinogens in the recent RoC GF. It would be more scientifically sound to fully utilize the large body of scientific research on fiber glass, which has shown that most glass fibers are biosoluble in animal inhalation studies do not produce fibrosis or cancer in well-conducted chronic inhalation studies. Only the special-purpose fibers, which are much more biodurable and produce cancer in well-conducted animal inhalation studies, should be classified as carcinogens by the NTP. This differentiation of glass fibers and carcinogen classification is in harmony with both the IARC and the EU directive. It also agrees with the recommendations of the NTP's own 2009 Expert Panel.

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